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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/732,847	12/09/2003	John G. Gribben	WYS-020.02	9329

25181 7590 05/01/2008

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EXAMINER	
GAMBEL, PHILLIP	

ART UNIT	PAPER NUMBER
1644	

MAIL DATE	DELIVERY MODE
05/01/2008	PAPER

Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Office Action Summary	Application No.	Applicant(s)	
	10/732,847	GRIBBEN ET AL.	
	Examiner	Art Unit	
	Phillip Gambel	1644	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE *3* MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *22 January 2008*.

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1,3 and 5-15* is/are pending in the application.

4a) Of the above claim(s) *5, 6, 9- 14* is/are withdrawn from consideration.

5)☐ Claim(s) *15* is/are allowed.

6)☒ Claim(s) *1,3,8* is/are rejected.

7)☒ Claim(s) *7* is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

1. Applicant's amendment, filed 01/22/2008, has been entered.

Claims 1 and 3 have been amended

Claims 2 and 4 have been canceled.

Claim 15 has been added.

Claims 1, 3 and 5-15 are pending.

Applicant's election of the species of "anti-B7-2 antibody as the second agent / blocking molecule" and "diabetes as the autoimmune disease" in the Reply to Restriction Requirement, filed 12/27/2006, has been acknowledged in the Office Action, mailed 03/22/2007.

Applicant's election with traverse of the species "wherein an autoantigen is not administered to the subject" the Reply to Restriction Requirement, filed 07/23/2007, has been acknowledged.

Given applicant's amended claims, filed 01/22/2008; the elected invention as it reads on "wherein an autoantigen is not administered to the subject" appears to be allowable, except for the outstanding rejection under obvious-type double patenting.

In the interest of compact prosecution, given that the elected invention appears allowable, this Office Action addresses "administering an autoantigen for autoimmune disease".

As indicated in the previous Office Action, the species "administering an autoantigen for autoimmune disease" raises issued under 35 USC 112, first paragraph, indicated herein.

Claims 1, 3 and 5-15 are pending.

Claims 5-6 and 9-14 have been withdrawn as being drawn to non-elected inventions and/or species.

Claims 1, 3, 7-8 and 15 are being acted upon as they read upon the elected invention and the additional species of "administering an autoantigen for autoimmune disease" as indicated above.

Applicant is invited to consider limiting withdrawn claim 5 to those "agents" recited in claim 6 to avoid issues under 35 USC 112, first paragraph, (as addressed previously with respect to "agents that inhibits a costimulatory signal in the T cell").

3. As indicated previously, the effective filing date of the instant claim is deemed to be the filing date of the priority application USSN 08/253,783, filed 06/03/1994.

4. Upon applicant's amended claims, filed 01/22/2008, the previous rejection under 35 U.S.C. 112, second paragraph, has been withdrawn.

5. Upon applicant's amended claims, filed 01/22/2008, the previous rejection under 35 U.S.C. 112, first paragraph, written description with respect to the recitation of recite "an agent which stimulates a CTLA4-associated apoptotic signal in the T cell" and "wherein the agent is an anti-CTLA monoclonal antibody" has been withdrawn.

6. Upon applicant's amended claims, filed 01/22/2008, the previous rejection under 35 U.S.C. 112, first paragraph, enablement has been withdrawn

7. Given that applicant's amended claims, filed 01/22/2008, has placed the elected invention with respect to applicant's election with traverse of the species "wherein an autoantigen is not administered to the subject" free of the prior art other than the obviousness-type double patenting rejection;
the following rejection is set forth in the interest of compact prosecution as it reads broadly on treating autoimmune disease "further comprising administering an autoantigen to the subject" (e.g., see claim 8).

8. This is a 35 U.S.C § 112, first paragraph, "written description" (and not new matter).

Claim 8 is rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention.

The specification broadly describes and the claims recite methods of inducing apoptosis in activated T cells as it reads on treating autoimmune disorders encompassing a method step that "further comprising administering an autoantigen to the subject" as part of the invention.

Pages 27-28 of the instant specification describes the following.

B. Autoimmune Diseases: Clonal deletion of T cells by induction of antigen specific T cell apoptosis may also be therapeutically useful for treating autoimmune diseases. Many autoimmune disorders are the result of inappropriate activation of T cells that are reactive against self tissue (i.e., reactive against autoantigens) and which promote the production of cytokines and autoantibodies involved in the pathology of the diseases. Preventing the activation of autoreactive T cells thus may reduce or eliminate disease symptoms. Administration of an agent that stimulates a CTLA4-associated apoptotic signal, such as an anti-CTLA4 antibody of the invention, which binds to an epitope on CTLA4 that induces T cell apoptosis can be used to delete autoreactive T cells, thereby inhibiting T cell responses and preventing production of autoantibodies or T cell-derived cytokines which may be involved in the disease process. Additionally, since autoreactive T cells can be eliminated rather than simply tolerized, long-term relief from the disease may be achievable.

To treat an autoimmune disorder, an agent that stimulates a CTLA4-associated apoptotic signal (e.g., CTLA4 ligand of the invention) is administered to a subject in need of treatment. Autoreactive T cells, previously activated by autoantigen in vivo, will be induced to undergo apoptosis upon antigenic stimulation by autoantigen in vivo. Alternatively, for autoimmune disorders with a known autoantigen, the autoantigen can be coadministered to the subject with the apoptotic agent. Since only activated T cells are eliminated by this treatment, resting T cells specific for other antigens should be unaffected by the treatment.

This method can be used to treat a variety of autoimmune diseases and disorders having an autoimmune component, including diabetes mellitus, arthritis (including rheumatoid arthritis, juvenile rheumatoid arthritis, osteoarthritis, psoriatic arthritis), multiple sclerosis, myasthenia gravis, systemic lupus erythematosis, autoimmune thyroiditis, dermatitis (including atopic dermatitis and eczematous dermatitis), psoriasis, Sjogren's Syndrome, including keratoconjunctivitis sicca secondary to Sjogren's Syndrome, alopecia areata, allergic responses due to arthropod bite reactions, Crohn's disease, aphthous ulcer, iritis, conjunctivitis, keratoconjunctivitis, ulcerative colitis, asthma, allergic asthma, cutaneous lupus erythematosus, scleroderma, vaginitis, proctitis, drug eruptions, leprosy reversal reactions, erythema nodosum leprosum, autoimmune uveitis, allergic encephalomyelitis, acute necrotizing hemorrhagic encephalopathy, idiopathic bilateral progressive sensorineural hearing loss, aplastic anemia, pure red cell anemia, idiopathic thrombocytopenia, polychondritis, Wegener's granulomatosis, chronic active hepatitis, Stevens-Johnson syndrome, idiopathic sprue, lichen planus, Crohn's disease, Graves opthalmopathy, sarcoidosis, primary biliary cirrhosis, uveitis posterior, and interstitial lung fibrosis.

However, applicant was not in possession of the claimed "autoantigens" as an element of the claimed methods in the absence of providing sufficient structural and functional characteristics of the species or genus of such "autoantigens" encompassed by the instant claim language, coupled with a known or disclosed correlation between function and structure.

Further, the autoimmune disorders would differ in autoantigens;
each autoimmune disorder would have multiple autoantigens; and
each autoimmune disorder would have different / multiple autoantigens playing a key role at different times during the course of an autoimmune disorder.

While pages 28-29 of the instant specification describes passive animal experimental models for treating EAE,
there is insufficient written description as to those "autoantigens" that would be applicable for administration in treating autoimmune disorders in humans, as broadly encompassed both in terms of "autoantigens" and "autoimmune disorders".

In reviewing immunotherapy of autoimmunity, Tisch et al. (PNAS 91: 437-438, 1994) teach that it is apparent that peptide- or antigen-specific T immunotherapy, when applied to a highly defined model of autoimmunity, can be effective. However it is unclear whether this approach is feasible in the prevention or treatment of spontaneous autoimmune disease such as multiple sclerosis, diabetes or arthritis, in which the target autoantigens are not known and a number of autoantigens appear to be involved in the disease process). Furthermore, it is unclear whether such immunotherapy can be used to treat an ongoing autoimmune response (which is the usual case) or whether it is effective only in terms of prevention. Generally, such diseases are diagnosed only after significant tissue damage has occurred. Similar arguments can be made for any immunotherapy (i.e. inflammation, cancer, pathogens) that requires specificity of antigen-specific receptors (i.e. antibodies or T cell receptors). Human diseases comprise multiple

epitopes or multiple immune responses that makes therapeutic intervention a major hurdle even for known diseases.

Also, note methods "further comprising administering an autoantigen to the subject" is distinguished from passive therapy with the claimed anti-CTLA4 antibody "wherein an autoantigen is not administered to the subject" because the skilled artisan does not need to know or posses the autoantigen in question.

Rather the skilled artisan simply relies upon the presence of the autoantigen already present in the patient with the autoimmune disorder.

The instant application has not provided a sufficient description showing possession of the necessary functional characteristics coupled with a known or disclosed correlation between function and structure, or by a combination of such identifying characteristics, sufficient to show the applicant was in possession of the genus of "autoantigens" over a broad range of autoimmune disorders.

Therefore, there is insufficient written description of the claimed genera of "autoantigens" over a broad range of autoimmune disorders in the absence of defining the relevant identifying characteristics such as the structure or other physical and/or chemical characteristics of the claimed genus.

Further, the Court has interpreted 35 U.S.C. §112, first paragraph, to require the patent specification to "describe the claimed invention so that one skilled in the art can recognize what is claimed. Enzo Biochem, Inc. v. Gen-Probe Inc, 63 USPQ2d 1609 and 1618 (Fed. Cir. 2002). In evaluating whether a patentee has fulfilled this requirement, our standard is that the patent's "disclosure must allow one skilled in the art 'to visualize or recognize the identity of' the subject matter purportedly described." Id. (quoting Regents of Univ. of Cal. v. Eli Lilly & Co., 43 USPQ2d 1398 (Fed Cir. 1997)).

The Guidelines for the Examination of Patent Applications Under the 35 U.S.C. 112, ¶ 1 "Written Description" Requirement make clear that the written description requirement for a claimed genus may be satisfied through sufficient description of a representative number of species by actual reduction to practice, reduction to drawings, or by disclosure of relevant, identifying characteristics, i.e., structure or other physical and/or chemical properties, by functional characteristics coupled with a known or disclosed correlation between function and structure, or by a combination of such identifying characteristics, sufficient to show the applicant was in possession of the genus .

It is not sufficient to define a genus without sufficient description of a representative number of species by actual reduction to practice, reduction to drawings, or by disclosure of relevant, identifying characteristics, i.e., structure or other physical and/or chemical properties, by functional characteristics coupled with a known or disclosed correlation between function and structure, or by a combination of such identifying characteristics.

In the absence of sufficient description of a representative number of species by actual reduction to practice, reduction to drawings, or by disclosure of relevant, identifying characteristics, the claimed invention is not described in such a way as to reasonably convey to one skilled in the relevant art that the inventors, at the time the application was filed, had possession of the claimed invention.

Vas-Cath Inc. v. Mahurkar, 19 USPQ2d 1111, makes clear that "applicant must convey with reasonable clarity to those skilled in the art that, as of the filing date sought, he or she was in possession of the invention. The invention is, for purposes of the written description inquiry, whatever is now claimed." (See page 1117.) The specification does not "clearly allow persons of ordinary skill in the art to recognize that [he or she] invented what is claimed." (See Vas-Cath at page 1116.). Consequently, Applicant was not in possession of the instant claimed invention. See University of California v. Eli Lilly and Co. 43 USPQ2d 1398.

The problem here is that the instant specification fails to provide a sufficient disclosure of which "autoantigens" across a broad range of autoimmune disorders are required for methods of treating autoimmunity with anti-CTLA4 antibodies "further comprising administering an autoantigen to the subject" in order "to induce apoptosis in an activated T cells in a subject, broadly encompassed by the claimed invention.

A skilled artisan cannot, as one can do with a fully described genera, visualize or recognize the identity of the members of the genus that exhibit this functional property.

Therefore, there is insufficient written description for genera of "autoantigens" across a broad range of autoimmune disorders in the claimed methods "further comprising administering an autoantigen to the subject" employing anti-CTLA4 antibodies that induce apoptosis in an activated T cells in a subject including in the treatment of autoimmunity", broadly encompassed by the claimed invention at the time the invention was made and as disclosed in the specification as filed under the written description provision of 35 USC 112, first paragraph.

Applicant has been reminded that Vas-Cath makes clear that the written description provision of 35 USC 112 is severable from its enablement provision. (See page 1115.)

Applicant is reminded that the amendment must point to a basis in the specification so as not to add any new matter. See MPEP 714.02 and 2163.06

9. Claims 1 and 3 are rejected under the judicially created doctrine of obviousness-type double patenting as being unpatentable over claims 1, 2, 4 and 8-11 of U.S. Patent No. 6,719,972.

Although the conflicting claims are not identical, they are not patentably distinct from each other because the patented claims encompass methods which employ the anti-CTLA4 antibodies that anticipate the instant anti-CTLA-4 antibodies, including characteristics that stimulate CTLA4-associated signal in T cells recited in the instant.

It does not appear that the claim language or limitations result in a manipulative difference in the method steps when compared to one another.

As filed 01/22/2008, applicant's request that the Examiner hold in abeyance all obviousness-type double patenting rejections based on said issued U.S. patent until allowable subjected matter is indicated, at which point applicant will consider filing a terminal disclaimer is acknowledged.

The rejection is maintained for the reasons of record.

Applicant is invited to file a terminal disclaimer and amend / cancel claims accordingly to place the instant application in condition for allowance.

11. Claim 15 is deemed allowable.

Claim 7 is objected to as being dependent upon a rejected base claim, but would be allowable if rewritten in independent form including all of the limitations of the base claim and any intervening claims.

Again, applicant is invited to file a terminal disclaimer and amend / cancel claims accordingly to place the instant application in condition for allowance.

12. Applicant's amendment necessitated the new ground(s) of rejection presented in this Office action. Accordingly, THIS ACTION IS MADE FINAL. See MPEP § 706.07(a). Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the date of this final action.

13. Any inquiry concerning this communication or earlier communications from the examiner should be directed to Phillip Gambel whose telephone number is (571) 272-0844. The examiner can normally be reached Monday through Thursday from 7:30 am to 6:00 pm. A message may be left on the examiner's voice mail service. If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Eileen O'Hara can be reached on (571) 272-0878.

The fax number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

/Phillip Gambel/

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April 27, 2008